Depression

Depression is one of leading causes of disability worldwide. It will affect 25% of people at least once in their lifetime (Hendrie & Pickles 2012) and with a mortality rate of 10% it’s one of the largest contributors to the worldwide burden of disease (Kern et al. 2012). Major Depression is characterized by a depressed mood and loss of interest, this is often accompanied by fatigue, abnormal appetite, irritability and difficulty concentrating (Croy et al. 2014; Kern et al. 2012). Though easily diagnosed from the persistence of these symptoms, there still lacks a fundamental understanding of the neurobiological cause and the most effective treatment (Krishnan & Nestler 2008).

The core brain regions involved in depression are the medial dorsolateral prefrontal cortex and limbic structures (Berton & Nestler 2006; George et al. 2013) and imaging and post mortem studies have demonstrated structural changes in these areas. There are three main hypotheses of the cause of depression: the monoamine, neuroendocrine and neurogenesis theories (Kern et al. 2012). Although there is strong evidence supporting all of these theories, research has yielded conflicting results, and as a result, the pathology in its entirety is still not fully understood.

1. Monoamine theory
The monoamine theory of depression relies on the efficacy of antidepressant medication, such as monoamine uptake or degradation inhibitors, which directly increase the levels of monoamines in the brain. The main monoamines targeted are serotonin, noradrenaline and dopamine (Delgado 2000). Additional evidence supporting this theory is that depleting these monoamines, for example with the drug reserpine, induces depression like symptoms, (Muller et al. 1955). However, this study has been criticised because the prevalence of subjects displaying depression following reserpine treatment was similar to the expected depression rate in the population and often these studies used patients with pre-existing mental disorders (Baumeister et al. 2003). Further analysis of the involvement of monoamines in depression has explored the possibility of receptor super and sub-sensitivity, and has suggested that adrenergic and serotonergic receptors may be desensitised in patients with depression (Elhwuegi 2004).

2. Neuroendocrine theory
Because stress is often associated with the onset of depression (Krishnan & Nestler 2008), hormonal changes have been investigated as a possible cause. The main neuroendocrine change observed in depression is in the hypothalamic-pituitary-adrenal (HPA) axis, which regulates the release and impact of stress hormones including adrenocorticotropic hormone (ACTH) and cortisol. Hyperactivation of this system has been recorded in depression (Bhagwagar et al. 2005) and some patients with depression have increased adrenal gland size caused by chronic corticotrophin secretion (Nemeroff et al. 1992).
3. Neurogenesis
The ability of the brain to generate new neurons (neurogenesis) is essential for healthy brain development, maintenance and function (Kempermann et al. 2004). Deficits in neurogenesis have been found in post-mortem tissue from patients with depression, although results are variable between studies, (Sahay & Hen 2007; Boldrini et al. 2009). Small sample sizes and antidepressant use are significant limitations of post-mortem data, which may be reason for insignificant or conflicting results. Nonetheless, analysis of the hippocampus, the main brain area involved in neurogenesis, has shown a decrease in hippocampal volume in patients with depression, supporting the hypothesis that there are fewer neurons being generated (Videbech & Ravnkilde 2004).

Reduced neurogenesis in humans has also been linked to a decrease in brain derived neurotrophic factor (BDNF), a protein responsible for the development and survival of neurons (Karege et al. 2005; Sen et al. 2008). This is relevant because chronic antidepressant treatment increases BDNF and in animal and human studies, has been shown to restore neurogenesis to normal levels (Brunoni et al. 2008; Boldrini et al., 2009).

4. Multiple factors contribute to the development of depression
Three of the major factors known to be involved in the development of depression have been outlined above. However, it is important to note that these mechanisms are likely to interact: For example, research has shown that both activation of glucocorticoid receptors in the HPA axis (Kim et al. 2004), and delivery of serotonin receptor antagonists (Radley & Jacobs 2002), reduce hippocampal neurogenesis. There are also theories involving altered circadian rhythm, immune disruption and a key role for genetic factors (Kern et al. 2012). This complexity, and most likely, variability between patients with depression is why discovering and applying appropriate and effective treatments is such a challenge.

5. Current Treatments and future directions
The most common treatments for depression are anti-depressant drugs. These drugs, the most common being selective serotonin reuptake inhibitors (SSRIs), primarily target monoamine deficiencies, (Berton & Nestler 2006). Such anti-depressant drugs are reasonably effective in cases of moderate to severe depression (up to 70%; Kern et al. 2012). However, there is little difference between drug and placebo responses in cases of mild depression (Khan et al. 2002), suggesting that other mechanisms need to be addressed.

Patients who do not respond to drugs are termed as having treatment resistant depression (TRD) (Hendrie & Pickles 2012) and one approach in treating such patients is to use neuromodulation (Holtzheimer & Mayberg 2012). The most extreme example is electroconvulsive therapy (ECT), which involves delivering electrical shocks to the brain to induce seizures. Although ECT has been effective in alleviating TRD, the major side effect of amnesia has led to investigation of other methods of neuromodulation (Holtzheimer & Mayberg 2012). One of these is repetitive transcranial magnetic stimulation (rTMS) which induces electrical currents in the brain by electromagnetic induction (Hallett 2007). This procedure is FDA-approved for the treatment of depression and can be highly targeted to particular brain regions, primarily the prefrontal cortex, resulting in fewer side effects and more tailored treatment options (George et al. 2013). Neuromodulation techniques represent an exciting new treatment method for those with TRD. Research is ongoing to determine the most effective stimulation parameters that lead to effective and long term alleviation of depression symptoms.
References:


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